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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/017,715	02/03/1998	HONGJUN JI	1488.0810003	8739

7590 05/07/2002

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	26

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/017,715	Ji et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *16-47, 50, 51, 53, and 57-78* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *16-42* is/are allowed.

6) ☒ Claim(s) *43-47, 50, 51, 53, and 57-78* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *25*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on January 17, 2002 has been entered.

2. Claims 10-12, 14, 15 and 79 have been canceled. Claims 16-47, 50, 51, 53 and 57-78 are pending and examined on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 44, 45 and 57-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 44 and 45 are drawn to an isolated polynucleotides comprising 100 and 250 contiguous nucleotides, respectively, of the coding region of SEQ ID NO:1 or the complement thereof. Claims 57-70 are drawn to polynucleotides comprising nucleic acids which encode amino acids sequences selected from the group consisting of amino acids 94-107 of SEQ ID NO:2 and amino acids 120-127 of SEQ ID NO:2. Claim 72 is drawn to an isolated polynucleotide comprising a nucleic acid encoding an amino acid sequence, wherein, except for one to thirty conservative amino acid substitutions, said amino acid is selected from the group consisting of

amino acids 1 to 127 of SEQ ID NO:2, amino acids 2-127 of SEQ ID NO:2 and the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit Number 97856. Claims 73-75 specify the number of amino acid substitutions are not more than 10, 5 and 3, respectively. Claim 76 is drawn to an isolated polynucleotide comprising a nucleic acid sequence encoding an amino acid sequence 95% or more identical to amino acids 1-127 of SEQ ID NO:2, amino acids 2-127 of SEQ ID NO:2, or the amino acid sequence encoded by the cDNA clone contained in ATCC Deposit Number 97856. Claim 77 is drawn to an isolated polynucleotide comprising a nucleic acid sequence which is 95% or more identical to nucleotides 15 to 392 of SEQ ID NO:1, or nucleotides 12 to 392 of SEQ ID NO:1.

The written description in this case only sets forth the polypeptide of SEQ ID NO:2, the polynucleotide of SEQ ID NO:1 and equivalent degenerative codon sequences and therefore the written description is not commensurate in scope with the claims drawn to variants of SEQ ID NO:1 (claim 77), polynucleotides encoding variants of SEQ ID NO:2 (claims 72-76), or polynucleotides comprising nucleic acids encoding small fragments of SEQ ID NO:2 (claims 57-70) or polynucleotides comprising 100 to 250 contiguous nucleotides of SEQ ID NO:1.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed. (See page 1117). The specification does not clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed. (See Vas-Cath at page 1116).

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

The instant claims are drawn to variants of SEQ ID NO:1, undisclosed polynucleotides comprising nucleic acids encoding two small fragments of SEQ ID NO:2, and polynucleotides encoding variants of SEQ ID NO:2. The specification teaches only SEQ ID NO:1 and

polynucleotides encoding the polypeptide of SEQ ID NO:2. With the exception of degenerate coding sequences as applied to SEQ ID NO:1, the specification does not give examples of defined polynucleotide variants or defined variants of SEQ ID NO:2 that would have the same function as the disclosed SEQ ID NO:1 or SEQ ID NO:2. On page 19, lines 21-25 of the specification it is stated:

> "It will be recognized in the art that some amino acid sequences of the BSG1 polypeptide can be varied without significant effect of the structure or function of the protein. If such differences in sequence are contemplated, it should be remembered that there will be critical areas on the protein which determine activity."

However, the specification does not identify or give examples of such critical areas. The substitution or deletion of amino acid residues to make a variant protein is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al (The Journal of Cell Biology, 1990, Vol. 111, pp. 2129-2138, cited in the Office Action of Paper No. 19, mailed May 10, 2001), the replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein. Lazar et al (Molecular and Cellular Biology, 1988, Vol. 8, pp. 1247-1252, cited in the Office action of Paper No. 19) discloses that the replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity of transforming growth factor alpha, while replacement with serine or glutamic acid sharply reduced the biological activity of TNF-alpha. These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. Clearly, it could not be predicted that a variant polynucleotide, polynucleotide encoding a variant polypeptide or a polynucleotide comprising only a small portion of the coding sequence of SEQ ID NO:2, would function as suggested and the specification provides nor guidance on how to use these variant polynucleotides.

With the exception of SEQ ID NO:1, polynucleotides consisting of SEQ ID NO:1, polynucleotides encoding SEQ ID NO:2 and degenerate coding sequences thereof, and

polynucleotides consisting of nucleic acids encoding amino acid residues 94 to 107 of SEQ ID NO:2 or amino acid residues 120-127 of SEQ ID NO:2, the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Lts., 18 USPQ2d 1016.

Furthermore, In The Regents of the University of California v. Eli Lilly (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that an adequate written description of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention..

The specification does not teach how to make variants of SEQ ID NO:1 or 2 beyond stating on page 20, lines 6-18, that conserved or non-conserved amino acids may be substituted, and the substituted amino acid residue may or may not be one encoded by the genetic code. This is insufficient to support the generic claims as provided by the Revised Interim Written Description Guidelines published in the January 5, 2001 Federal Register at Volume 66, Number 4, pages 1099-1111.

Therefore only an isolated DNA molecule comprising a DNA sequence consisting of SEQ ID NO:1, polynucleotides comprising nucleotide residues 12-392 and 15-392 of SEQ ID NO:1, polynucleotides encoding SEQ ID NO:2, polynucleotides encoding residues 2-127 of SEQ ID

NO:2, degenerative coding sequences of SEQ ID NO:2 and residues 2-127 of SEQ ID NO:2 and isolated DNA molecules consisting of a nucleic acid encoding residues 94-107 of SEQ ID NO:2 and residues 120-127 of SEQ ID NO:2, and the polynucleotides comprising the amino acid sequence encoded by the cDNA clone contained in ATCC deposit No. 97856, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 43, 46, 50, 51, 53 and 78 are rejected under 35 U.S.C. 102(b) as being anticipated by Adams et al (WO 93/16178) as evidenced by Accession Number AAQ61421.

Claim 43 is drawn to an isolated polynucleotide comprising 50 contiguous nucleotides of the coding region of SEQ ID NO:1 or the complement thereof. Claim 46 specifies the nucleotide is DNA. Claims 53, and 51 embody the host cell and vector comprising said isolated polynucleotide. Claim 50 is drawn to a method of producing a vector comprising the insertion of said isolated polynucleotide into a vector. Claim 78 is drawn to an isolated polynucleotide comprising a nucleic acid wherein said nucleic acid hybridizes under stated conditions to SEQ ID NO:1 and wherein said nucleic acid is 50 or more nucleotides long.

Adams et al disclose the isolated cDNA of SEQ ID NO:2396 which comprises 80 contiguous nucleotides of SEQ ID NO:1 as evidenced by Accession Number AAQ61427, a vector and a host cell comprising SEQ ID NO:2396 and a method of inserting SEQ ID NO:2396 into said vector. The 80 contiguous nucleotides of SEQ ID NO:2396 would hybridize to SEQ ID NO:1 under the stated conditions.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 43, 46, 50, 51, 53, 78 and 47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al (WO 93/16178) in view of Sambrook et al (Molecular Cloning, A Laboratory Manual, 2nd Edition 1989, pages 10.27-10.28).

The teachings of Adams et al as applied to the embodiments of claims 43, 46, 50, 51, 53, 78 are stated supra. Claim 46 is drawn to the specific embodiment of RNA as the polynucleotide. Adams et al do not teach an isolated RNA comprising 50 contiguous ribonucleotides of SEQ ID NO:1. Sambrook et al teach the generation of radiolabeled mRNA from vectors comprising s nucleic acids.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to make an RNA comprising 80 contiguous nucleotides of SEQ ID NO:1. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Adams et al on the usefulness probes which hybridize

to SEQ ID NO: 2396 for mapping the chromosomal location of the expressed gene, for an identification of tissue type, and for facilitating the mapping of disease associated genes and the efficacy of using radiolabeled RNA as a probe as taught by Sambrook et al.

9. All other rejections and objection as stated in Paper No. 22 are withdrawn.

Conclusion

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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Patent Examiner, Group 1642
April 2, 2002

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